Exhibit 155

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Refractory Migraine

Continuous Opioid Therapy (COT) is Rarely Advisable for Refractory Chronic Daily Headache: Limited Efficacy, Risks, and Proposed Guidelines

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Intractable pain, headache or otherwise, is a devastating and life-controlling experience. The need to effectively and aggressively control pain is a fundamental tenet of clinical care. In the past several years, increasing advocacy for continuous opioid therapy has become an important, if not controversial, theme in the development of treatment guidelines and teaching programs. Ironically, the increasing willingness of physicians to prescribe scheduled opioids for their headache and pain patients has occurred in the absence of compelling data demonstrating efficacy or long-term safety. To the contrary, two meta-analyses on chronic noncancer pain (CNCP) and one long-term uncontrolled study on headache patients demonstrate a relatively small number of patients benefiting from the treatment. Recent neuroscience data on the effects of opioids on the brain raise serious concern for long-term safety and also provide the basis for the mechanism by which chronic opioid use might induce progression of headache frequency and severity. Significant adverse effects, including influence on sexual hormonal balances, physical and psychological dependence, the development of opioid-induced hyperalgesia, and cardiac arrhythmia and sudden death that can be seen with standard dosages of methadone, make a strong argument against widespread use of continuous opioid therapy (COT) in otherwise healthy young and middle-aged headache patients.

We believe that COT should be used in rare circumstances for chronic headache patients, and propose initial guidelines for selecting patients and monitoring treatment. The physician should be well versed in the details of opioid prescribing, administration, and monitoring, and should be prepared to discontinue opioids when clinical justification, patient behavior, or failure to achieve therapeutic goals make discontinuance necessary.

Key words: chronic daily headache, guidelines, opioids, refractory headache

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Despite the best available treatments from the realms of pharmacotherapy, cognitive-behavior therapy (including biofeedback), physical therapy, evidence-based complementary medicine, anesthesiological intervention, and inpatient treatment protocols, some chronic daily headache (CDH) patients remain refractory. For this intractable group, a compassionate, ethical approach to treatment requires that we consider alternatives with the potential for relief of suffering, which could include continuous opioid therapy (COT).[1,2]

There has been a strong trend in the pain management field to advocate aggressively for opioids as scheduled prophylactic medication for both cancer and chronic noncancer pain (CNCP). In a survey of 161 primary care physicians in the University of California, San Francisco/Stanford Collaborative Research Network, 65% indicated some willingness to prescribe schedule II opioids (eg, sustained release morphine) for CNCP patients.[3] Although drugs with long half-lives (eg, methadone) or sustained release

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formulations are often favored, the efficacy and safety profiles of long-acting vs short-acting opioids have not been shown to differ significantly.[4]

Pain is now treated as a *fifth vital sign*,[5] with placards in emergency departments and hospital rooms encouraging patients to speak up about their pain. The Joint Commission on Accreditation of Hospitals requires healthcare facilities to assess and monitor pain, which in practical terms may often involve aggressive use of opioids, not only for acute pain and occasional rescue, but also on a scheduled basis. However, the extent to which identifying pain as a fifth vital sign has actually led to improved pain management has been questioned.[6] Some have raised a red flag that the fifth vital sign concept may minimize the risk of overmedicating vs undermedicating pain, citing clinical cases of significant opioid-related respiratory depression, sometimes leading to death.[7]

In this article, we summarize our experience with COT for intractable headache, including our transformation from optimism about the potential to our current position that COT should rarely be administered to headache patients. COT should only be considered for those who meet strict criteria, and following rigorous procedures to assess response, adherence, and adverse effects. Moreover, prior to initiating COT, the prescribing physician should detail an explicit plan with the patient for opioid discontinuation if and when this becomes appropriate or necessary. This article is an expansion of an article we previously published in *Headache Currents*.[8] Here we first review the evidence for efficacy of sustained opioids in the treatment of headache and other forms of CNCP, followed by a review of adverse effects. We conclude by proposing guidelines for patient selection and formal treatment monitoring.

RESULTS OF LONG-TERM OBSERVATIONAL STUDY OF COT FOR REFRACTORY CDH

In 1992, we initiated a formal COT program for carefully selected, refractory patients with CDH, with a plan to carefully monitor outcomes over the long term. All enrolled patients had been in our practice for at least 2 years prior to starting COT, and failed to sustain benefit from available evidence-based prophylactic pharmacotherapy and behavioral intervention. The majority had refractory chronic migraine, with a level of intractability that far exceeded the definition proposed by Schulman and others in this special section of the journal.[9] We were initially encouraged by our preliminary data, as reflected in published abstracts.[10-13] In a published abstract, Rothrock also reported "good improvement" with 15 of 30 patients with COT (methadone), and "modest improvement" in 10.[14] However, when we assessed outcomes after 3 years or longer for 160 consecutively enrolled patients, we found that 74% either failed to benefit or were discontinued for clinical reasons.[15]

Although 26% of the initially enrolled patients might be classified as good responders – based on 50% or better improvement in an index of severe headache activity compared with the 2-year baseline – this did not correlate with the type of global report of improvement on which physicians may often rely to justify continuing COT. Patients reported significantly higher levels of global improvement attributed to the opioid program (mean = 70% on a visual analog scale or VAS) than was actually supported by the medical record (mean = 46%, $P < .00001$). In fact, there was no statistically significant correlation between global reports of improvement on the VAS and the ostensibly more objective medical record data. We now estimate that only 10-15% (16-32) of the initially enrolled patients actually experienced meaningful sustained improvement from COT, when functioning and other collateral sources of data (eg, significant others) were included in the assessment.[15]

Furthermore, global reports of pain improvement attributed to COT did not necessarily correlate with meaningful improvement in functioning. Our published report was based on 160 patients who had started COT at least 3 years previously—the intent-to-treat group, of which 70 remained on COT for 3 years or longer. The Figure depicts previously unpublished data from a larger group, including those in the published study and additional patients enrolled in the COT program for less than 3 years. Although some patients improved in functional outcomes, a substantial percentage of those who reported at least 50% improvement attributed to opioids on the VAS continued to report significant functional impairment

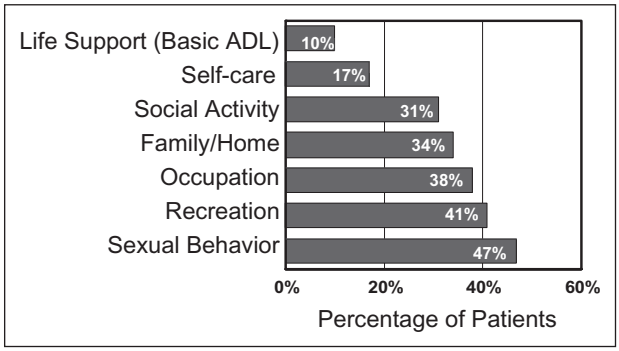

Figure.—Percentage of patients who rated themselves as significantly disabled on each of the 7 scales of the Pain Disability Index (defined as a rating of 6 or higher, where 10 = "total disability"), despite patient's report of >50% pain improvement attributed to continuous opioid therapy on a visual analog scale (N = 155). ADL = activities of daily living.

based on the Pain Disability Index, a set of rating scales ranging from 0 ("no disability") to 10 ("total disability") on 7 functional dimensions.[16-18]

We believe that some of this reported disability may be due to decreased motivation directly related to frequent opioid use. The lack of evidence for increased functioning was one reason COT was discontinued for many patients. Although not quantified, we encountered a number of patients who discontinued opioids under protest and then later told us how glad they were to be off opioids – that they had not realized the extent of opioid-related impairment, lack or motivation, or anhedonia they had experienced while on COT.

Problem drug behavior (dose violations, lost prescriptions, multisourcing) occurred in 50% of the 70 patients who remained on COT for 3 years or longer.[15] These issues were typically uncovered through detailed chart audits, collateral contact with significant others, or with other physicians. They were not necessarily revealed during standard clinical visits with experienced physicians, nurses, and psychologists. In most cases, compassionate confrontation on the problem behavior was sufficient to reset treatment on a level course, although problems often continued until identified and confronted.

EFFICACY OF COT FOR CNCP

Meta-analyses.—At the time of this writing, the most recently available meta-analysis of the efficacy and safety of opioids in randomized controlled trials for CNCP pain by Furlan and others searched MEDLINE, EMBASE, and CENTRAL databases through May 2005 for any opioid administered by oral or transdermal routes or rectal suppositories. Included were 41 randomized trials involving 6019 patients: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis, or back pain), 12% neuropathic pain (post herpetic neuralgia, diabetic neuropathy, or phantom limb pain), 7%, fibromyalgia, and 1% mixed pain. They found that 90% of the trials were either funded by or had one or more coauthors affiliated with the pharmaceutical industry. They found no trials of transdermal or rectal routes of administration, nor opioid infusion programs for chronic pain. There were no studies limited to headache patients.

The mean duration of treatment was 5 weeks (range 1-16), well below the expected duration of treatment for scheduled opioids in clinical practice. Despite the relative shortness of the trials, one-third of the participants abandoned treatment. Dropout rates averaged 33% in the opioid groups and 38% in the placebo groups. Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. However, in head-to-head comparisons with opioids, other drugs produced significantly better functional outcomes.[19]

Kalso et al analyzed all available randomized, placebo-controlled trials through September 2003. Fifteen trials met inclusion criteria, including 11 studies (1025 patients) comparing oral opioids with placebo. Mean pain relief with opioids was about 30%, with only a minority appearing to benefit from long-term treatment. In one study reviewed, only 20% of patients had still had relief with oral morphine after one year. Five studies found no significant difference between opioid or placebo treatment. Despite some benefit from short-term use of opioids, only 44% of 388 patients who were offered continued COT elected to remain on opioids for periods ranging between 7 and 24 months.[20] Others have subsequently noted that "The evidence base for this type of pain management is meager because the needed randomized controlled trials, *which ideally should last for several years*, have not been performed" (italics added).[21]

There is expected overlap between the cumulative Furlan meta-analysis[18] and the earlier Kalso meta-analysis.[19] Furlan compared the efficacy of opioids vs placebo in the 20 randomized controlled trials published through 2002 with the additional 8 trials published in 2003 and 2004. Opioid efficacy was comparable and stable; the additional trials did not change the conclusions.[18]

The above 2 meta-analyses were limited to randomized controlled trials. Noble and others published a meta-analysis of long-term efficacy and adverse events for CNCP patients treated with opioids for at least 6 months, including open-label studies. In a search of 11 databases through April 7, 2007, 17 studies (3,079 patients) met the inclusion criteria. They concluded that weak evidence suggests that oral and intrathecal opioids reduce pain long-term for patients who benefit short-term with minimal adverse effects. There was insufficient data from transdermal studies to quantify pain relief. They also identified high dropout rates due to adverse effects (32.5% for oral opioids) or insufficient pain relief (11.9%, oral opioids).[22]

Epidemiological Research.—In a national epidemiological study of noncancer pain in Denmark, opioid usage was significantly associated with reports of higher pain levels (moderate/severe or very severe), poor self-rated health, unemployment, greater use of the healthcare system, and a lower health-related quality of life, as reflected on all items on the Medical Outcome Study – Short Form (SF-36). As with all cross-sectional epidemiological research, causal relationships cannot be established. However, the authors note that "it is remarkable that opioid treatment of long-term/chronic noncancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life, and improved functional capacity."[23]

Efficacy Related to Age.—In one recent retrospective chart review of 206 patients with CNCP, only adults over age 60 years showed a significant reduction in visual analog pain scales from the start of opioid therapy until discharge from the clinic, with a daily dose 54% lower than younger patients. However, the amount of change was modest, from 6.9 (±0.3 on a 10-point scale) to 5.3 (±0.3, $P < .01$).[24] We have been unable to find any published studies to date of the efficacy – or long-term safety – of frequent opioids for children, adolescents, or young adults. Opioid tolerance, and therefore receptor alterations, appears to develop more much more rapidly in younger patients,[24] a finding supported by experimental studies on age-related tolerance in animals.[25]

ADVERSE EFFECTS OF OPIOIDS

Prevalence of Opioid-Related Adverse Effects and Impact on Sustaining Treatment.—The most common adverse effect stemming from opioid administration is nausea, sometimes associated with emesis, occurring in 26% of 8855 patients in a retrospective cohort study of patients receiving short-term opioids in 35 community-based and tertiary hospitals.[26] In the Furlan meta-analysis of short-term randomized controlled studies noted above, only constipation and nausea were statistically significant.[18] However, when all adverse effects are combined, 77% of 104 CNCP patients receiving opioids at a National Health Service hospital pain clinic in London reported side effects. While 72.5% reported receiving some benefit, 86.5% had discontinued opioids at some point in their treatment, and 65% had done so permanently.[27]

Transformation to CDH and Medication Overuse Headache.—One of the great advances in the field of headache science was the recognition that the frequent use of certain medications – centrally acting analgesics, ergotamine tartrate, triptans, and butalbital-containing compounds – can contribute significantly to the transformation to CDH and intractability until the implicated drugs are discontinued.[28,29] Prospective epidemiological research has identified the *frequent use* of analgesics (*once a week or more*) as a significant risk factor for chronic pain 11 years later. This relative risk (RR) is greatest for headache disorders, including chronic migraine (RR = 13.3) and chronic nonmigrainous headache (RR = 6.2). However, the RR is also significantly elevated for chronic neck pain (RR = 2.4) and low back pain (RR = 2.3). The RR for CDH predicted by analgesic *overuse* (ie, daily) was 19.6 for migraine and nonmigrainous headache combined.[30] Daily use of opioids for nonheadache conditions (eg, to control bowel motility in colectomy patients) increases the risk of episodic

migraine transforming to CDH.[31] The frequent use or overuse of certain classes of analgesics and abortive medications (eg, opioids, barbiturate containing analgesics, triptans) may be the primary risk factor leading to CDH.[32] However, the frequency of headache episodes, even in the absence of medication overuse, is also a predictor of the transformation to CDH.[33]

The terms to describe the overuse of acute treatment medication have evolved, from "rebound" and "drug-induced headache" to "medication overuse headache" (MOH).[28,29] The definition of MOH is still undergoing revision, but is currently based on the frequency of use of specific abortive and analgesic agents, no longer requiring recovery to episodic headaches within a 2-month period after withdrawal in order to confirm the MOH diagnosis.[34] Research and clinical experience continue to highlight the benefits of withdrawal from overused medication and recovery of therapeutic responsiveness when the offending medications are discontinued,[35] as well as the potential time frame for recovery – from 2-3 months or less[35,36] to as long as 10 months in isolated cases.[36] Long-term outcome studies have also identified high rates of relapse after drug withdrawal for patients receiving pharmacological prophylaxis: 31% within 6 months of withdrawal, and from 21% (triptans) to 71% (analgesics) at 4 years,[37] although this may be mitigated by adding behavioral coping skills for pain management, such as biofeedback.[38,39]

Opioid-Induced Hyperalgesia.—The past decade has witnessed a growing body of evidence in support of *opioid-enhanced hypersensitivity to pain* in both human and animal studies, frequently referred to as *opioid-induced hyperalgesia* (OIH).[40-42] This apparently paradoxical phenomenon – one of the apparent principal mechanisms underlying MOH – can occur with even brief periods of administration. For example, the intraoperative administration of fentanyl or remifentanil enhances the extent and duration of postoperative pain.[43] Recent studies have shown that neural plasticity associated with the development of opioid *tolerance* may activate a *pronociceptive* mechanism that could counteract the analgesic effect of opioids.[42] Studies with animal models suggest genetic variation as a significant factor contributing to differences in the propensity to develop OIH.[44]

Several factors have been identified as mediating OIH. Sustained morphine exposure increases activity of sensory neuropeptides (calcitonin gene-related peptide [CGRP] and substance *P*) and their downstream signaling messengers (prostaglandins, lipoxengenase metabolites, and endocannibinoids).[45,46] Whether OIH might be mitigated by CGRP antagonists currently under development is yet to be determined. Sustained morphine also increases neurokinin-1 (NK-1) receptor expression in the spinal dorsal horn.[47] NK-1 receptor expressing neurons play a critical role in sustained morphine-induced neuroplastic changes which underlie spinal excitability reflected as thermal and tactile hypersensitivity to peripheral stimuli, and to reduced antinociceptive actions of spinal morphine.[48] Opioid-induced activation of neuropeptide FF (NPFF) receptors has also been shown to play a critical modulating role in OIH and associated opioid tolerance.[49]

Cholecystokinin (CCK) is upregulated in the rostral ventromedial medulla (RVM) during persistent opioid exposure. CCK is both antiopioid and pronociceptive, and activates descending pain facilitation mechanisms from the RVM. The neuroplastic changes elicited by opioid exposure reflect adaptive changes to promote increased pain transmission and consequent diminished opioid efficacy (ie, tolerance).[50,51] Opioids induce glial cells to release proinflammatory cytokines, including tumor necrosis factor, that play a role in compromised opioid analgesia and adverse effects including tolerance, dependence, and reward.[52-54] Opioids have also recently been implicated in immune response suppression, although the relationship between activity in the immune system and pain is not well understood.[55]

In clinical practice, OIH is often marked by allodynia and worsening pain despite increasing doses of opioids, a red flag. The patient may also experience a diffuse spreading of what was initially experienced as more focal pain, a common experience for many patients when episodic migraine transforms to MOH.

Subsequent Intractability to Nonopioid Analgesia for Migraine.—For years, clinicians have suspected that overuse of certain drugs rendered their patients refractory to other appropriate treatment. For migraine sufferers, even intermittent prior exposure to

opioids may impede the efficacy of nonopioid analgesics. In a study by Jakubowski and others, between 64% and 71% of migraine sufferers achieved freedom from acute migraine pain and allodynia within one hour of ketorolac infusion. The only factor they uncovered to predict failure to respond to ketoralac was a history of opioid treatment in the nonresponders. The authors question whether opioids might contribute to long-term sustained headache intractability, even in nonactive opioid users – some of these patients had only used opioids intermittently in the past.[56] However, it remains also possible that many patients with a prior opioid history had a more aggressive or refractory disorder than those who had not previously received opioids. Although further research on prior use of opioids and failure to respond to treatment is needed, the study raises a yellow flag of caution.

Opioid Abuse and Dependence Following COT for Noncancer Pain.—The prevalence of problem drug behavior in CNCP patients receiving opioids has been reported as high as 24 out of 100 randomly selected patients in an interventional pain medicine setting, with frequent abuse in 12%.[57] In a prospective study of the initial evaluation of 100 patients at an interventional pain clinic, 35 had at least one drug abuse behavior uncovered in the urine drug screen, including 12 who denied using opioids and who had no opioid prescriptions, and 23 using illicit drugs.[58]

Manchikanti et al assessed the presence of depression (59%), anxiety (64%), and somatization disorder (30%) in a series of 500 consecutive CNCP patients receiving scheduled opioids. Drug abuse was significantly higher in patients with depression (12%) than in those without depression (5%). Current illicit drug use was higher in women with depression (22%) than either women with no depression (14%) or men with or without depression (12%). Current illicit drug use was also higher in men with somatization disorder (22%) than men without (9%).[59]

Edlund and others investigated risk factors for the development of diagnosed opioid dependence/abuse in 15,160 patients prescribed opioids for CNCP in the Veterans Administration healthcare system in the USA. The strongest predictor was a history of nonopioid substance abuse, with an odds ratio (OR) of 2.34, $P < .005$. Comorbid mental health disorders were moderately strong predictors (OR = 1.46, $P < .005$). They note that the prevalence of mental health disorders (45.3%) was much higher than the prevalence of nonopioid substance abuse (7.6%), suggesting that psychiatric disorders place more of the CNCP population at risk for opioid abuse than is the case for comorbid nonopioid substance abuse. Males, younger adults, and individuals with greater supplies of prescription opioids were more likely to develop opioid abuse or dependence.[60] Others have reported an "addiction rate" of 2.8% in CNCP patients receiving sustained opioids.[27]

Respiratory Depression and Sudden Cardiac Death.—The most serious and potentially fatal opioid-related adverse effects in pain management are respiratory depression and cardiac arrhythmias.[7] In a study of 8855 CNCP patients receiving opioids (morphine, meperidine, or fentanyl), the overall rate of respiratory depression was 1.5%. When compared with adults age 45 or less, the RR for respiratory depression increased significantly with age: RR = 2.8 for ages 61-70, RR = 5.4 for ages 71-80, and RR = 8.7 for those over 81 years.[26] Early respiratory depression may manifest itself in drowsiness, yawning, or reports of difficulty breathing. In more significant cases, the patient may report confusion, with decreased pulse oxygen. The clinician should ask about early symptoms, evaluate further if there is reason for suspicion, and consider reducing the dose or discontinuing opioids.

In November 2006, the United States Food and Drug Administration issued a Health Alert for health professionals on risks of death, cardiac arrhythmias (eg, QT interval prolongation), and narcotic overdose associated with methadone.[61] Methadone may pose a particular risk given its long half-life and accumulation in fat tissue over time.[62] During a 4-year period, Chugh et al prospectively evaluated autopsy data from the medical examiner in the Portland, Oregon metropolitan area, for all consecutive investigations of sudden cardiac death. They compared deceased patients with a therapeutic blood level of methadone (<1 mg/L) and case comparison subjects with no identified methadone, excluding those with recreational drug use or any drug overdose. Based on a significantly lower rate of cardiac abnormalities in the

methadone group (23%) than the comparison group (60%, $P = .002$), they concluded that methadone was "implicated as a cause of death, even at normal therapeutic levels." The most common indication for methadone use in the deceased patients was for pain control (55%).[63]

Reductions in Sex Hormones.—Sustained opioids induce reductions in sex hormones in both men and women. Sustained opioids inhibit adrenal androgen production.[64,65] Dehydroepandrosterone (DHEA)-dehydroepiandroisterone sulfate (DHEAS) deficiency is associated with fatigue, depression, weakness, and sexual dysfunction. In a study of nonhospitalized male and female patients using sustained action oral or transdermal opioids for nonmalignant pain, Daniell found DHEAS values to be significantly lower in opioid users than nonopioid controls in a dose-related pattern. DHEAS was below age-specific norms in 67% of opioid uses vs 8% of controls, and below the lowest detection limit in 29% of opioid users vs 1% of controls. In contrast, adrenocorticotropic hormone (ACTH) levels remained unaffected by opioids. The findings were unrelated to body mass index or concurrent hormonal replacement therapy.[64] Clinical correlates include reports of erectile dysfunction in men and hypogonadism, although paradoxically the only 2 studies in the Furlan meta-analysis found that patients receiving COT actually reported improved sexual behavior on the PDI.[19] Clinically, we have seen false pregnancies, failure to menstruate, and galactorrhea in women, and breast enlargement in men. The National Institute of Health is currently undertaking a human study of opioid use and endocrinological changes.

Opioids During Pregnancy.—Although the occasional use of opioids for controlling severe pain during pregnancy may be relatively safer for the fetus than some other alternatives, there may be reason for caution in their use on a frequent or scheduled basis. Opioids can have neurotoxic on the brains of young animals that are significant in perinatal administration.[66] A prospective study of 34 drug-exposed (opioids and nicotine) and 42 reference infants (nicotine only) one year after delivery found significantly lower scores on scales of locomotor development, hearing, speech, and intellectual performance, in addition to a higher incidence of neurological abnormalities in the opioid-exposed group.[67] These differences were independent of whether the child was living in a foster home or with the biological parents. A Norwegian study of postnatal development of children exposed to opioids in utero, found significantly lower scores on the Bayley Scales at one year, and the McCarthy Scales at 4.5 years, with special weaknesses in the areas of visual-motor and perceptual abilities.[68] These children were reportedly raised under condition of "minimal postnatal social risk" with adoptive or foster parents.

Admittedly, extrapolation of these findings to mothers receiving COT for pain control only, under close medical supervision, must be approached with caution. For example, of the 34 mothers taking opioids in the first study, 12 were using without medical control and 22 were in a methadone maintenance program.[67] Nevertheless, such studies raise a flag of caution. Similar research is yet to be done with prospective mothers on COT for CNCP, and little is known of minimal dose levels at which possible delayed adverse effects on infant development may occur.

Neurocognitive Functioning.—Opioid treatment of patients with mild uncomplicated traumatic brain injury has recently been found to be associated with reduced learning.[69] Opioids seem to be more likely to worsen cognitive performance during the first few hours after a given dose, and during the first few days of use, particularly on timed performance in psychomotor tasks.[70] A prior review of the literature found inconsistent results regarding cognitive performance decrements in chronic pain patients receiving opioids for more than 3 days when compared with healthy volunteers. Relatively few differences have been found between pre- and postopioid performance for chronic pain patients, or with the performance of a comparable pain population not taking opioids.[70]

Depression, Anxiety, and Stress.—Treatment of postconcussive patients with opioids has also been associated with increased depression, anxiety, and stress.[69] Respiratory depressive effects of the endogenous opioid system (and by extension, exogenous opioids) may play a role in triggering panic attacks associated with air hunger, by reducing the "suffocation alarm threshold."[71] However, studies in advanced cancer patients have shown reductions in depression

Table.—Proposed Guidelines for Continuous Opioid Therapy for Refractory Chronic Daily Headache: Patient Selection Criteria and Formal Treatment Monitoring Requirements

A. All of the following (1-5) are required
   1. The patient is an adult over age 30 years
   2. Moderate to severe, convincing pain and functional compromise occurring more that 20 days/month
   3. A history of reliable and compliant medication usage and related behavior
   4. Prescribing physicians have at least 4 clinical visits over several months' time in which there are personal, direct treatment encounters with the eligible patient prior to administration of opioids. (Physicians must know the patient and have a reasonable understanding of the level of intractability, compliance, maturity, and psychological makeup.)
   5. The prescribing physician has competence, knowledge, and experience in the use of the scheduled opioid.

B. At least one of the following (1-5) must also apply
   1. Convincing refractoriness to aggressive, advanced, comprehensive treatment, which should include:
      a. Ruling out and treating MOH (if present)
      b. Appropriately aggressive pharmacotherapy
      c. Cognitive-behavioral pain management
      d. Interventional treatment, if indicated
      e. Diagnostic review to rule out organic and pathological disturbances
   2. The presence of convincing, serious adverse effects from otherwise appropriate medications, thus severely limiting available treatments
   3. Senior individuals (eg, >65 years old) where other treatments are ineffective or pose safety concerns (Note that relative risk of respiratory depression rises significantly with age, and that seniors may reach efficacy with significantly lower doses)
   4. Individuals with significant medical comorbidities in whom other options for treatment are not available or contraindicated
   5. Pregnancy, in which other acceptable treatments are ineffective and pain control is required (Note possible developmental delay with sustained opioids – coordinate care with patient's obstetrician)

C. Any of the following (1-6) would generally disqualify
   1. Severe Axis I DSM-IV diagnosis, or multiple diagnoses of moderate severity (exception – some patients with mood disorders attributed to their medical condition may experience significant improvement in depression with pain relief)
   2. Past or present true addictive disease (exception – nondrinking, rehabilitated alcoholic)
   3. Axis II Cluster B personality disorders (significant antisocial, borderline, histrionic, or narcissistic traits)
   4. Presence of moderate to severe somatoform features
   5. Active psychosis or Axis II Cluster A personality disorders (paranoid, schizoid, schizotypal)
   6. Family environment with known substance abuser (exception – history of long-term sustained remission following treatment participation)

D. A formal treatment monitoring system for appropriate use, safety, efficacy, and functional impact must be in place
   1. Written, signed, and witnessed pretreatment agreement
      a. Compliance expectations
      b. Collateral discussions with family member or significant other
      c. Collateral discussions with other treatment professionals
      d. Agreement and plan for safe withdrawal from COT in the event the prescribing physician or patient believes that discontinuation is in patient's best interest
   2. Pretreatment and ongoing urine drug screens
   3. Regular office visits every 1-2 months, including periodic contact with family members or significant others to assess efficacy, functioning, and adverse effects
   4. Periodic psychological consultation to assess compliance, efficacy, functioning, psychological benefit or adverse effects, adherence to self-help and cognitive-behavioral pain management techniques
   5. Accurate calculation of dose and pill counts coordinated with frequency of visits
   6. Formal assessment of efficacy and functional impact at each visit
   7. Periodic communication with all treating professionals
   8. Pretreatment and periodic updates (through state registries, when available) of all scheduled drugs that a patient has been prescribed and filled in the past year

COT = continuous opioid therapy; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision;[73] MOH = medication overuse headache.

and anxiety with opioid therapy (transdermal fentanyl),[72] possibly due to enhanced pain control.

PROPOSED GUIDELINES AND CRITERIA FOR COT FOR REFRACTORY HEADACHE PATIENTS

We have previously proposed guidelines for the prescription of daily scheduled opioids for refractory CDH patients, shown in the Table.[8] The guidelines are directly based on both our long-term observational outcome study described above,[15] and our clinical experience with intractable patients from a national referral base.[15] Patient selection criteria are based on the risk of adverse effects as noted above.

DISCUSSION

Pain causes desperation, and desperately painful patients seek any means of relief possible, at times at any cost or possible (even probable) risk.[8] As physicians, our compassion and desire to relieve pain must be balanced with the Hippocratic dictum of *first do no harm*, even in the most refractory cases. Opioids are powerful drugs. We must balance the potential for enhanced pain control against risk, from idiopathic aggravation of the headache condition (MOH, OIH) to other possible adverse effects on health and safety, functioning, and quality of life.

We are particularly concerned with the overuse of opioids in adolescents and young adults. Requiring that patients reach the age of 30 before any consideration of COT is a conservative safety recommendation. There is recent MRI evidence of continuing human brain development through adolescence into young adulthood.[74-76] The long-term impact of opioids on the developing brain is unknown. In the absence of evidence to the contrary, there appears to be reason for concern about use of frequent opioids in younger people. Patients with a potentially shortened life span from pain secondary to terminal illness (eg, cancer) would be an obvious exception,[77,78] but we believe chronic headache – which needs aggressive treatment – is not in the same category or a justification for opioids in the young.

We see large numbers of patients in our inpatient program who have been on COT for years, with a progressive cycle of breakthrough pain, escalating doses of opioids, with further pain progression, and psychiatric decompensation. In our long-term observational study, the level of improvement one month after starting COT was a significant predictor of long-term outcome, although this was by no means absolute. Even in those with an excellent initial response to treatment, the level of control declined significantly over the next 3 years.[15] COT may provide some patients with a limited window of relief, but in our experience is difficult to maintain over the long run.

We believe that sustained use of opioids – including not only COT, but at frequencies greater than one or 2 days/week as rescue medication – should be confined to rare cases, and systems of care and medical settings that can provide careful patient selection, psychological profiling and monitoring, with a plan for discontinuing opioids when treatment fails to meet prospectively determined goals for significant relief, improved functioning, and enhanced quality of life.

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